PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/415

A1

(11) International Publication Number: **WO 99/61020**

(43) International Publication Date: 2 December 1999 (02.12.99)

(21) International Application Number: PCT/US99/11490

(22) International Filing Date: 21 May 1999 (21.05.99)

(30) Priority Data:
60/086,494 22 May 1998 (22.05.98) US

(71) Applicant: AVANIR PHARMACEUTICALS [US/US]; 9393 Towne Centre Drive #200, San Diego, CA 92121 (US).

(72) Inventors: SIRCAR, Jagadish; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). RICHARDS, Mark, L.; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). CAMPBELL, Michael, G.; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US). MAJOR, Michael, W.; Avanir Pharmaceuticals, 9393 Towne Centre Drive #200, San Diego, CA 92121 (US).

(74) Agent: ALTMAN, Daniel, E.; Knobbe, Martens, Olson & Bear, LLP, 16th floor, 620 Newport Center Drive, Newport Beach, CA 92660 (US).

(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: BENZIMIDAZOLE ANALOGS AS DOWN-REGULATORS OF IgE

(57) Abstract

This invention relates to a family of diacyl benzimidazole analogs, which are inhibitors of the IgE response to allergens. These compounds are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic.

BENZIMIDAZOLE ANALOGS AS DOWN-REGULATORS OF IgE

Background of the Invention

This invention relates to small molecule inhibitors of the IgE response to allergens that are useful in the treatment of allergy and/or asthma or any diseases where IgE is pathogenic.

An estimated 10 million persons in the United States have asthma, about 5% of the population. The estimated cost of asthma in the United States exceeds $6 billion. About 25% of patients with asthma who seek emergency care require hospitalization, and the largest single direct medical expenditure for asthma has been inpatient hospital services (emergency care), at a cost of greater than $1.6 billion. The cost for prescription medications, which increased 54% between 1985 and 1990, was close behind at $1.1 billion (Kelly, *Pharmacotherapy* 12:13S-21S (1997)).

According to the National Ambulatory Medical Care Survey, asthma accounts for 1% of all ambulatory care visits, and the disease continues to be a significant cause of missed school days in children. Despite improved understanding of the disease process and better drugs, asthma morbidity and mortality continue to rise in this country and worldwide (U.S. Department of Health and Human Services; 1991, publication no. 91-3042). Thus, asthma constitutes a significant public health problem.

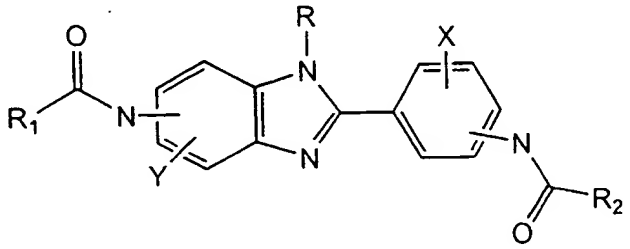
The pathophysiologic processes that attend the onset of an asthmatic episode can be broken down into essentially two phases, both marked by bronchoconstriction, that causes wheezing, chest tightness, and dyspnea. The first, early phase asthmatic response is triggered by allergens, irritants, or exercise. Allergens cross-link immunoglobulin E (IgE) molecules bound to receptors on mast cells, causing them to release a number of pre-formed inflammatory mediators, including histamine. Additional triggers include the osmotic changes in airway tissues following exercise or the inhalation of cold, dry air. The second, late phase response that follows is characterized by infiltration of activated eosinophils and other inflammatory cells into airway tissues, epithelial desquamonon, and by the presence of highly viscous mucus within the airways. The damage caused by this inflammatory response leaves the airways "primed" or sensitized, such that smaller triggers are required to elicit subsequent asthma symptoms.

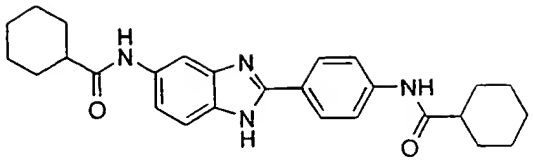
and allergic asthma in particular (Duplantier and Cheng, *Ann. Rep. Med. Chem.* 29:73-81 (1994)). Thus, compounds that lower IgE levels may be effective in treating the underlying cause of asthma and allergy.

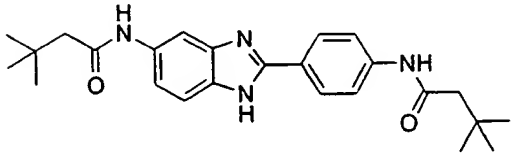
None of the current therapies eliminate the excess circulating IgE. The hypothesis that lowering plasma IgE may reduce the allergic response, was confirmed by recent clinical results with chimeric anti-IgE antibody, CGP-51901, and recombinant humanized monoclonal antibody, rhuMAB-E25. Indeed, three companies, Tanox Biosystems, Inc., Genentech Inc. and Novartis AG are collaborating in the development of a humanized anti-IgE antibody (BioWorld® Today, February 26, 1997, p. 2) which will treat allergy and asthma by neutralizing excess IgE. Tanox has already successfully tested the anti-IgE antibody, CGP-51901, which reduced the severity and duration of nasal symptoms of allergic rhinitis in a 155-patient Phase II trial (Scrip #2080, Nov 24, 1995, p.26). Genentech recently disclosed positive results from a 536 patient phase-II/III trials of its recombinant humanized monoclonal antibody, rhuMAB-E25 (BioWorld® Today, November 10, 1998, p. 1). The antibody, rhuMAB-E25, administered by injection (highest dose 300 mg every 2 to 4 weeks as needed) provided a 50% reduction in the number of days a patient required additional "rescue" medicines (antihistimines and decongestants), compared to placebo. An NDA filing for this product is projected to be in the year 2000. The positive results from anti-IgE antibody trials suggest that therapeutic strategies aimed at IgE down-regulation may be effective.

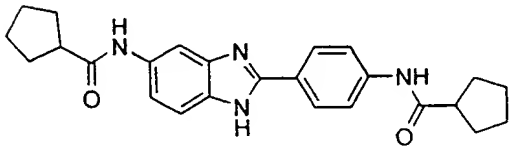
Summary of the Invention

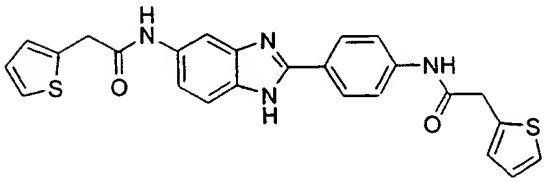
The present invention discloses a family of related compounds for use in the treatment of a condition associated with an excess IgE level. The benzimidazole inhibitors of IgE in accordance with the present invention are represented by the generic formula:

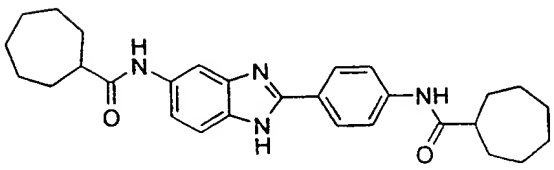


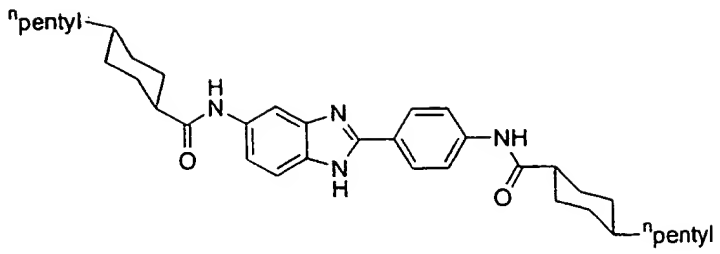


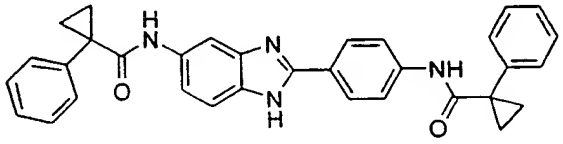


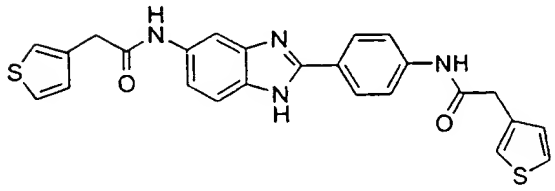


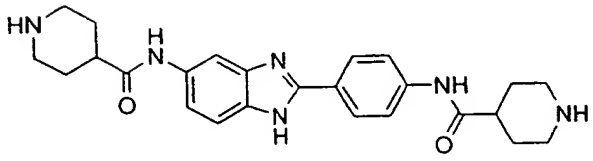


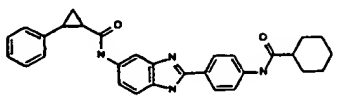


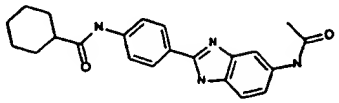

npentyl
H
N
O
N
N
H
NH
O
npentyl

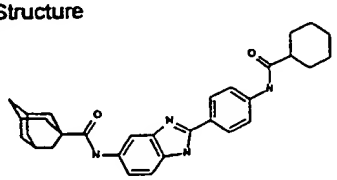

H
N
O
N
N
H
NH
O

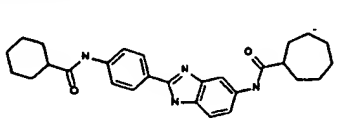

S
H
N
O
N
N
H
NH
O
S

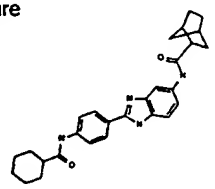

HN
H
N
O
N
N
H
NH
O
NH

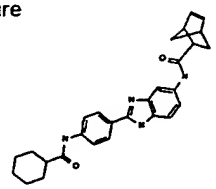
Structure	BIIM
	$C_{30}H_{30}N_4O_2$
	CLOGP 6.28

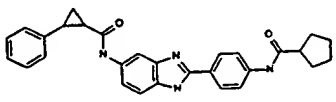
Structure	BIIN
	$C_{22}H_{24}N_4O_2$
	CLOGP 4.52

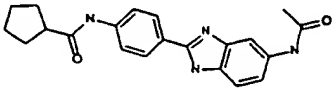
Structure	BIIO
	$C_{31}H_{36}N_4O_2$
	CLOGP 7.18

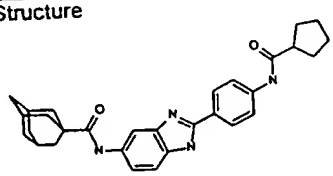
Structure	BIIP
	$C_{28}H_{34}N_4O_2$
	CLOGP 7.11

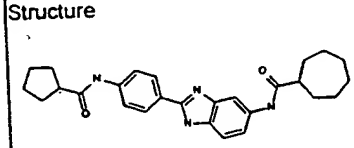
Structure	BIIQ
	$C_{28}H_{32}N_4O_2$
	CLOGP 6.30

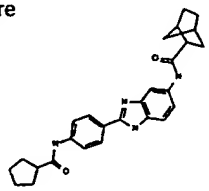
Structure	BIIR
	$C_{28}H_{30}N_4O_2$
	CLOGP 5.82

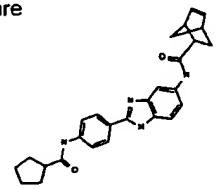
Structure	BIJM
	$C_{29}H_{28}N_4O_2$
	CLOGP 5.72

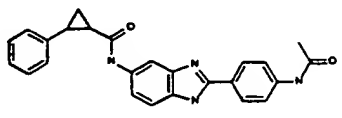
Structure	BIJN
	$C_{21}H_{22}N_4O_2$
	CLOGP 3.96

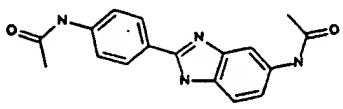
Structure	BIJO
	$C_{30}H_{34}N_4O_2$
	CLOGP 6.62

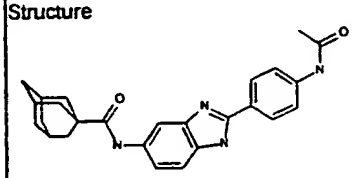
Structure	BIJP
	$C_{27}H_{32}N_4O_2$
	CLOGP 6.55

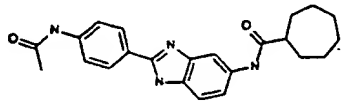
Structure	BIJQ
	$C_{27}H_{30}N_4O_2$
	CLOGP 5.75

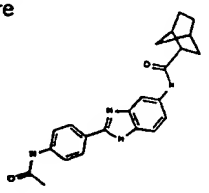
Structure	BIJR
	$C_{27}H_{28}N_4O_2$
	CLOGP 5.26

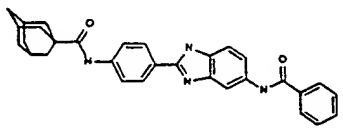
Structure	BINM
	$C_{25}H_{22}N_4O_2$
	CLOGP 4.25

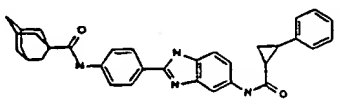
Structure	BINN
	$C_{17}H_{16}N_4O_2$
	CLOGP 2.49

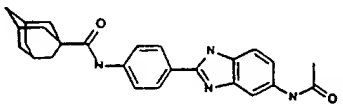
Structure	BINO
	$C_{26}H_{28}N_4O_2$
	CLOGP 5.15

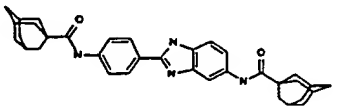
Structure	BINP
	$C_{23}H_{26}N_4O_2$
	CLOGP 5.08

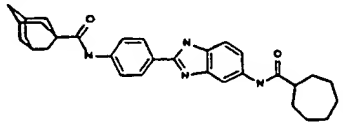
Structure	BINQ
	$C_{23}H_{24}N_4O_2$
	CLOGP 4.27

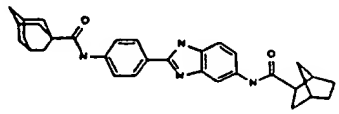
Structure	BINR
	$C_{31}H_{30}N_4O_2$
	CLOGP 3.79

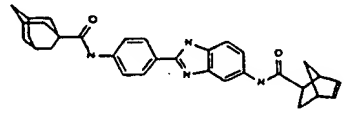
Structure	BIOM
	$C_{34}H_{34}N_4O_2$
	CLOGP 6.91

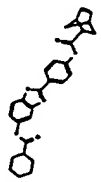
Structure	BION
	$C_{26}H_{28}N_4O_2$
	CLOGP 5.15

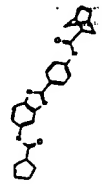
Structure	BIOO
	$C_{35}H_{40}N_4O_2$
	CLOGP 7.81

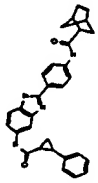
Structure	BIOP
	$C_{32}H_{38}N_4O_2$
	CLOGP 7.74

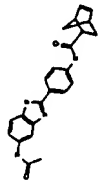
Structure	BIOQ
	$C_{32}H_{36}N_4O_2$
	CLOGP

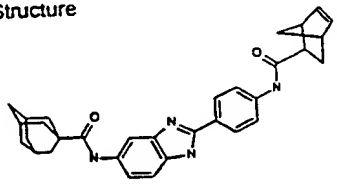
Structure	BIOR
	$C_{32}H_{34}N_4O_2$
	CLOGP

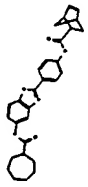
Structure	BIRI
	$C_{28}H_{30}N_4O_2$
	CLOGP 5.82

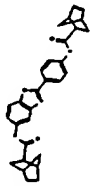
Structure	BIRJ
	$C_{27}H_{28}N_4O_2$
	CLOGP 5.26

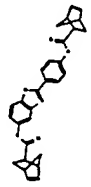
Structure	BIRM
	$C_{31}H_{28}N_4O_2$
	CLOGP 5.55

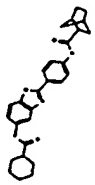
Structure	BIRN
	$C_{23}H_{22}N_4O_2$
	CLOGP 3.79

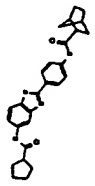
Structure	BIRO
	$C_{32}H_{34}N_4O_2$
	CLOGP 6.45

Structure	BIRP
	$C_{29}H_{32}N_4O_2$
	CLOGP 6.38

Structure	BIRQ
	$C_{29}H_{30}N_4O_2$
	CLOGP 5.58

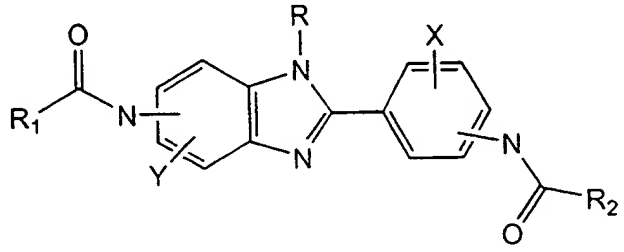
Structure	BIRR
	$C_{29}H_{28}N_4O_2$
	CLOGP 5.09

Structure	BIQI
	$C_{28}H_{32}N_4O_2$
	CLOGP 6.30

Structure	BIQJ
	$C_{27}H_{30}N_4O_2$
	CLOGP 5.75

CH_2Ph, and $CH_2C_6H_4$-F(p-). R_1 and R_2 are independently selected from the group consisting of alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, and substituted adamantyl, where the substitutions are selected from the group consisting of alkyl, aryl, CF_3, CH_3, OCH_3, OH, CN, COOR and COOH.

In accordance with another aspect of the present invention, there is disclosed a method of treating a mammal having a condition associated with an excess IgE level. The method comprises administering to the mammal an amount of a compound sufficient to reduced IgE levels in the mammal. The compound has the formula:



X and Y are independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$. R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7, C_4H_9, CH_2Ph, and $CH_2C_6H_4$-F(p-). R_1 and R_2 are independently selected from the group consisting of alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, and substituted adamantyl, where the substitutions are selected from the group consisting of alkyl, aryl, CF_3, CH_3, OCH_3, OH, CN, COOR and COOH.

In a variation of the above-disclosed method, at least one additional active ingredient may be administered in conjunction with the administration of the compound. The additional active ingredient may be combined with said compound in a pharmaceutically acceptable diluent and co-administered to the mammal. The additional active ingredient may be a short-acting β_2-

twice, and maintained in DMEM supplemented with 10% FBS, 100 U/ml penicillin, 100 μg/ml streptomycin and 0.0005% 2-mercaptoethanol. Spleen cell cultures were established (2-3 million cells/ml, 0.2 ml/well in quadruplicate, 96-well plates) in the presence or absence of DNP-KLH (10 ng/ml). Test compounds (2 μg/ml and 50 ng/ml) were added to the spleen cell cultures containing antigen and incubated at 37° C for 8 days in an atmosphere of 10% CO_2.

Culture supernatants were collected after 8 days and Ig's were measured by a modification of the specific isotype-selective ELISA assay described by Marcelletti and Katz (*Supra*). The assay was modified to facilitate high throughput. ELISA plates were prepared by coating with DNP-KLH overnight. After blocking with bovine serum albumin (BSA), an aliquot of each culture supernatant was diluted (1:4 in phosphate buffered saline (PBS) with BSA, sodium azide and Tween 20), added to the ELISA plates, and incubated overnight in a humidified box at 4° C. IgE levels were quantitated following successive incubations with biotinylated-goat antimouse IgE (b-GAME), AP-streptavidin and substrate.

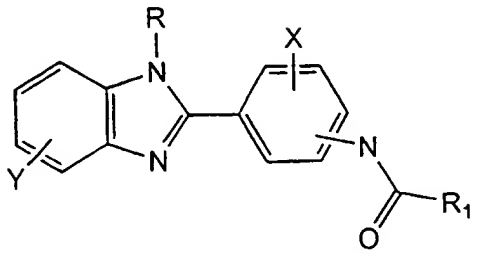
Antigen-specific IgG1 was measured similarly, except that culture supernatants were diluted 200-fold and biotinylated-goat antimouse IgG1 (b-GAMG1) was substituted for b-GAME. IgG2a was measured in ELISA plates that were coated with DNP-KLH following a 1:20 dilution of culture supernatants and incubation with biotinylated-goat antimouse IgG2a (b-GAMG2a). Quantitation of each isotype was determined by comparison to a standard curve. The level of detectability of all antibody was about 200-400 pg/ml and there was less than 0.001% cross-reactivity with any other Ig isotype in the ELISA for IgE.

In Vivo Assay

Compounds found to be active in the *ex vivo* assay (above) were further tested for their activity in suppressing IgE responses *in vivo*. Mice receiving low-dose radiation prior to immunization with a carrier exhibited an enhanced IgE response to sensitization with antigen 7 days later. Administration of the test compounds immediately prior to and after antigen sensitization, measured the ability of that drug to suppress the IgE response. The levels of IgE, IgG1 and IgG2a in serum were compared.

Female BALB/cByj mice were irradiated with 250 rads 7 hours after initiation of the daily light cycle. Two hours later, the mice were immunized i.p. with 2 μg of KLH in 4 mg alum. Two to seven consecutive days of drug injections were initiated 6 days later on either a once or twice

Another related genus is the monoacylated variation illustrated below:



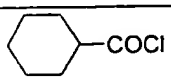
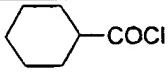
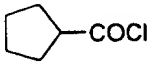
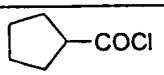
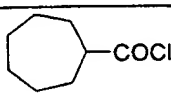
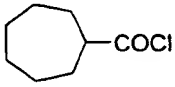
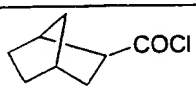
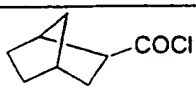
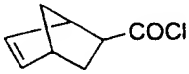
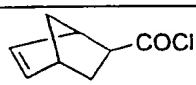
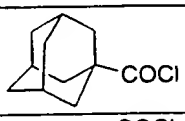
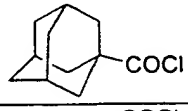
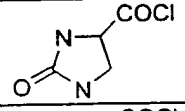
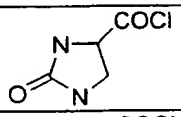
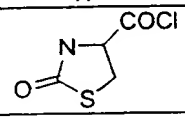
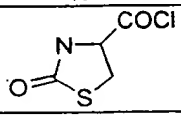
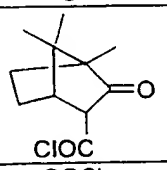
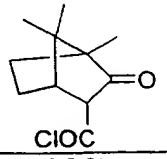
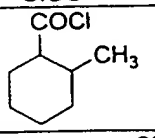
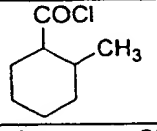
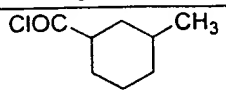
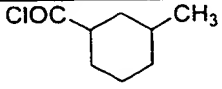
X is selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$. Y is selected from the group consisting of mono, di, and tri substituted H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$. R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7, C_4H_9, CH_2Ph, and $CH_2C_6H_4$-F(p). R_1 is selected from the group consisting of alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like. Substitutions are alkyl, aryl, CF3, CH3, OCH_3, OH, CN, COOR, COOH and the like.

Synthesis of the Combinatorial Library

The diacyl benzimidazole compounds of the present invention were prepared using the following synthesis reactions, wherein the desired acid chlorides are selected from the R1 and R2 groups provided in the Table.

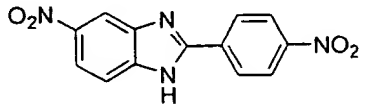
to stir at 3.4 atm pressure under H_2 atmosphere for 4 h. Upon completion of reaction as observed via TLC, the reaction mixture was filtered through celite and the solvent was removed under reduced pressure to afford 979 mg of crude residue.

TABLE

	R1		R2
A		A	
B		B	
C		C	
D		D	
E		E	
F		F	
H		H	
I		I	
J		J	
K		K	
L		L	

Syntheses of Symmetrical Diamides

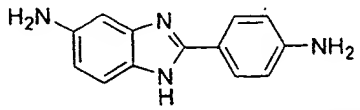
The symmetrical diacyl benzimidazole compounds of the present invention were generally prepared from 2-(4-aminophenyl)-5-aminobenzimidazole, which was obtained by reduction of 2-(4-nitrophenyl)-6-nitrobenzimidazole.



2-(4-nitrophenyl)-6-nitrobenzimidazole

The dinitro benzimidazole was prepared as follows: a mixture of 4-nitrophenylenediamine (6.4g, 41.83 mmol) and 4-nitrobenzoic acid (7.86 g, 47 mmol) was dissolved in $POCl_3$ (250 ml) and heated to reflux for 2 h. The reaction mixture was cooled, poured on to ice, and stirred for 30 min. The resulting solid was filtered and washed with methanol and sodium bicarbonate to remove unreacted acid and allowed to dry overnight to give the desired product as a brown solid (5.8 g). The product was characterized by electrospray mass spectroscopy (mp >300° C).

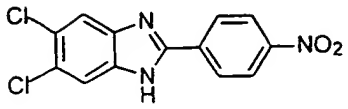
2-(4-Aminophenyl)-5-aminobenzimidazole was prepared by suspending the above solid (75 g) in THF (75 ml), to which was added Pd-C (10% Pd by weight). The flask was purged with hydrogen and stirred under a balloon of hydrogen over night. TLC and MS showed starting material was still present so the reaction was allowed to continue over the weekend. TLC indicated complete reaction, the reaction was filtered through celite and washed with methanol. The solvent was removed under reduced pressure to give a dark brown solid (0.37 g) that was used without further purification.



2-(4-aminophenyl)-5-aminobenzimidazole

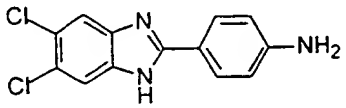
Alternatively, the 2-(4-aminophenyl)-5-aminobenzimidazole was prepared by the following reduction: 2-(4-nitrophenyl)-6-nitrobenzimidazole (8.9 g, 31 mmole) was suspended in concentrated HCl (100 ml) to which was added stannous chloride (42.3 g 180 mmole). The

cautiously poured onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



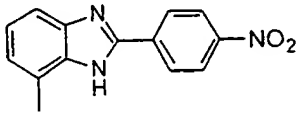
2-(4-nitrophenyl)-5,6-dichloro benzimidazole

2-(4-Aminophenyl)-5,6-dichloro benzimidazole was prepared by dissolving 1 g of the above nitrobenzimidazole in 30% $Na_2S \cdot 9H_2O$ (20 ml) with stirring at RT for 21 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



2-(4-Aminophenyl)-5,6-dichloro benzimidazole

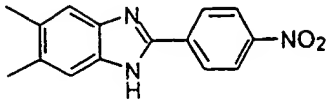
2-(4-aminophenyl)-7-methyl benzimidazole was synthesized from 2-(4-nitrophenyl)-7-methyl benzimidazole, which was prepared by mixing 1,2-diamino-3-methylbenzene (1.24 g, 10.0 mmole) with 4-nitrobenzoic acid (1.69 g, 9.8 mmole), dissolved in $POCl_3$ (10 ml), and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



2-(4-nitrophenyl)-7-methyl benzimidazole

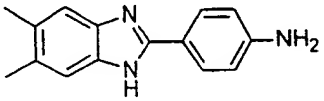
2-(4-Aminophenyl)-7-methyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole in 30% $Na_2S \cdot 9H_2O$ (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were

onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.



2-(4-nitrophenyl)-5,6-dimethyl benzimidazole

2-(4-Aminophenyl)-5,6-dimethyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole (31.1) in 30% $Na_2S \cdot 9H_2O$ (20 ml) with stirring at RT for 4.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



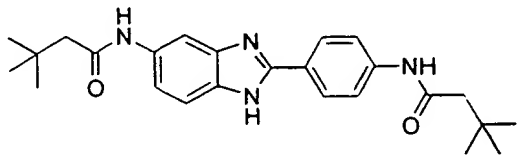
2-(4-aminophenyl)-5,6-dimethyl benzimidazole

The subsequent preparation of symmetrical diamides was accomplished by one of the following methods:

Method A: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) was suspended in THF (5 ml) to which was added DIEA (2.5 mmole) and mixture cooled to –78° C. To the above cooled mixture was added the acid chloride (2.5 mmole) and let warm to RT overnight. Water (2 ml) is added to the reaction and extracted with EtOAc. The combined organic extracts were combined washed with $NaHCO_3$ (aq.) and concentrated under reduced pressure. The resulting residue was purified on silica gel (hexanes/EtOAc or $MeOH/CH_2Cl_2$) or reverse phase HPLC (CH_3CN/H_2O).

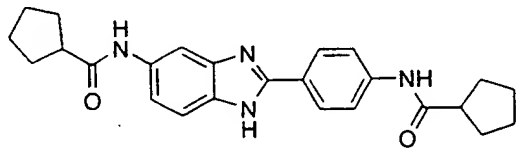
Method B: 2-(4-Aminophenyl)-6-aminobenzimidazole (1 mmole) and DMAP (cat.) was dissolved in pyridine (5 ml). To the above solution was added the acid chloride (2.5 mmole) and the reaction stirred overnight at 60° C. The reaction was cooled to room temperature and water added to precipitate the product. The resulting solid was collected by filtration with the solid

(2) Bis-t-butylacetyl benzimidazole was prepared by Method A from 2-(4-aminophenyl)-6-amino-benzimidazole (0.195 g, 0.87 mmole) and t-butylacetyl chloride (0.302 ml, 0.292 g, 2.175 mmol). The resulting solid (42.3 mg) was purified by preparative HPLC.



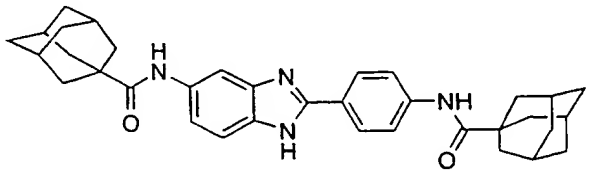
(2)

(3) Bis-cyclopentylcarbonyl benzimidazole was prepared by Method A from 2-(4-aminophenyl)-6-amino-benzimidazole (0.195 g, 0.87 mmole) and cyclopentylcarbonyl chloride (0.227 ml, 0.228 g, 2.175 mmol). The resulting solid (42.3 mg) was purified by preparative HPLC.



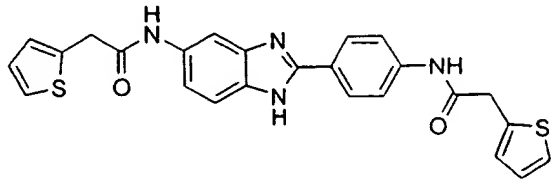
(3)

(4) Bis-adamantylcarbonyl benzimidazole was prepared by Method C from 2-(4-aminophenyl)-6-amino-benzimidazole (0.500 g, 2.23 mmole) and adamantylcarbonyl chloride (1.063 g, 5.35 mmol). The resulting solid was purified by preparative HPLC to give about 100 mg of 97% pure material.



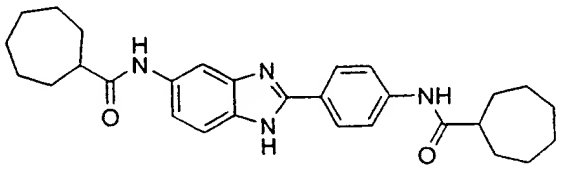
(4)

(0.660 ml, 0.860 g, 5.35 mmol). The resulting solid was purified on silica gel (5% MeOH in CH_2Cl_2). HPLC shows the product is 92% pure.



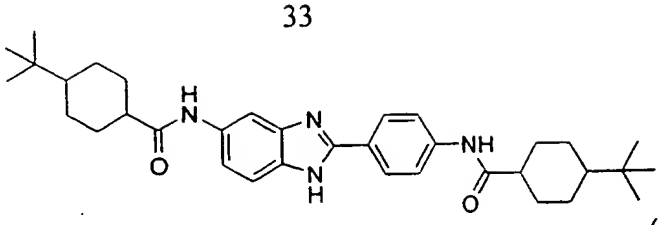
(8)

(9) Bis-cycloheptanecarbonyl benzimidazole was prepared by method C from 2-(4-aminophenyl)-6-amino-benzimidazole (0.500 g, 2.23 mmole) and cycloheptanecarbonyl chloride (0.610 ml, 0.634 g, 5.35 mmol). The resulting solid was purified by preparative HPLC to give a solid that was 98.8% pure. The cycloheptanecarbonyl chloride was synthesized as follows: cycloheptane carboxylic acid (1.37 ml, 1.42 g, 10 mmole) was added to a dried 25 ml round bottom flask and purged with N_2. To the flask was added oxalyl chloride (7.5 ml, 2 M in CH_2Cl_2) *via* syringe followed by one drop DMF. The reaction was stirred at RT overnight and the reaction concentrated under vacuum. Methylenechloride (5 ml) was added and concentrated under vacuum to remove residual oxalyl chloride (repeated 5 times).



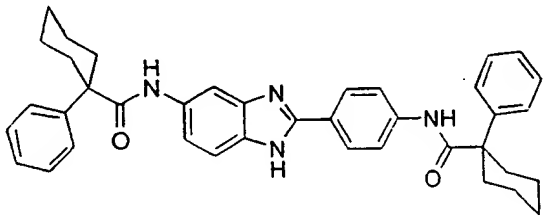
(9)

(10) Bis-(N-trifluoroacetylproline) benzimidazole was prepared by method A except that CH_2Cl_2 used as solvent from 2-(4-aminophenyl)-6-amino-benzimidazole (0.448 g, 2.0 mmole) and (s)-(-)-N-trifluoroacetylproline chloride (42.0 ml, 0.1 M in CH_2Cl_2). The resulting solid was purified on silica gel (5% MeOH in CH_2Cl_2). HPLC showed the product was 98.5% pure.



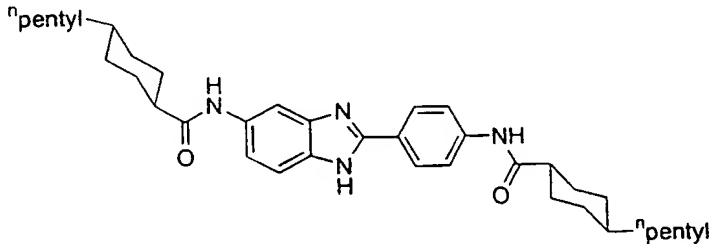
(13)

(14) Bis-1-phenylcyclohexyl carbonyl benzimidazole was prepared by method C from 2-(4-aminophenyl)-6-amino-benzimidazole (0.467 g, 2.08 mmole) and 1-phenyl-cyclohexylcarbonyl chloride (1.046 g). The resulting solid was purified on silica gel (5% MeOH in CH_2Cl_2). HPLC showed the product was 93.3% pure.



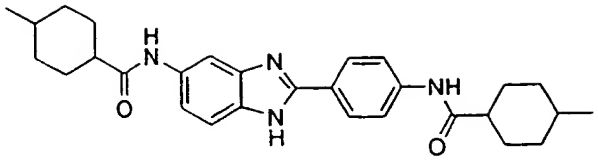
(14)

(15) Bis-trans-4-pentylcyclohexyl carbonyl benzimidazole was synthesized as follows: oxalyl chloride (1.07 ml, 2 M in CH_2Cl_2) was added to trans-4-pentylcyclohexyl carboxylic acid (0.424 g, 2.14 mmole) followed by one drop DMF. The mixture was allowed react at RT for 1 hour. To the above solution was added 2-(4-aminophenyl)-6-amino-benzimidazole (0.200 g, 0.89 mmole) in pyridine (2 ml). The



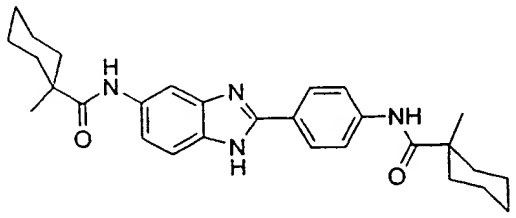
(15)

reaction was heated to 60° C overnight. The reaction was cooled and the precipitate filtered and washed with $NaHCO_3$ and hexanes. The resulting solid was purified by preparative HPLC to yield a solid which was >99% pure.



(18)

(19) Bis-1-phenylcyclohexyl carbonyl benzimidazole was synthesized as follows: oxalyl chloride (1.07 ml, 2 M in CH_2Cl_2) was added to 1-methylcyclo hexanecarboxylic acid (0.305 g, 2.14 mmole) followed by one drop DMF. The mixture was allowed to react at RT for 1 hour. To the above solution was added 2-(4-aminophenyl)-6-amino-benzimidazole (0.200 g, 0.89 mmole) in pyridine (2 ml). The reaction was heated to 60° C overnight.

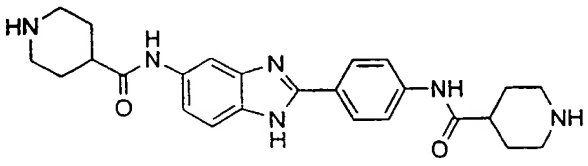


(19)

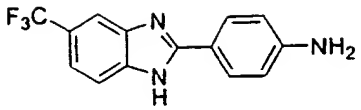
The reaction was cooled and the precipitate filtered and washed with $NaHCO_3$ and hexanes. The resulting solid was purified by preparative HPLC to give a solid that was >99% pure.

(20) Bis-bicyclo[2.2.1]heptane-2-carbonyl benzimidazole was prepared as follows: oxalyl chloride (1.07 ml, 2 M in CH_2Cl_2) was added to bicyclo[2.2.1] heptanecarboxylic acid (0.305 g, 2.14 mmole) followed by one drop DMF. The mixture was allowed to react at RT for 1 hour. To the above solution was added 2-(4-aminophenyl)-6-amino-benzimidazole (0.200 g, 0.89 mmole) in pyridine (2 ml). The reaction was heated to 60° C overnight. The reaction was cooled and the precipitate filtered and washed with $NaHCO_3$ and hexanes. The resulting solid was purified by preparative HPLC to give a solid that was 68% pure.

(23) Bis-4-nipecotamide benzimidazole was produced as follows: Bis-N-boc-4-nipecotamide benzimidazole (0.400 g) was dissolved in 1:1 TFA:CH_2Cl_2 (4 ml) at -20° C overnight. The solvent was removed under vacuum and water added, frozen on dry ice and lyophilized to dryness. The Boc-protected benzimidazole was synthesized as follows: oxalyl chloride (2.82 ml, 2 M in CH_2Cl_2) was added to N-Boc-nipecotic acid (1.293 g, 5.64 mmole) followed by one drop DMF. The mixture was allowed to react at RT for 1 hour. To the above solution was added. 2-(4-aminophenyl)-6-amino-benzimidazole (0.500 g, 2.24 mmole) in pyridine (5 ml). The reaction was heated to 60° C overnight. The reaction was cooled and the precipitate filtered and washed with $NaHCO_3$ and hexanes. The resulting solid was found to be >99% pure by HPLC.

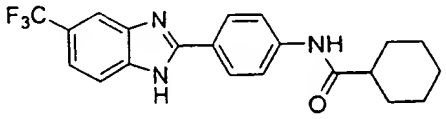


(23)



(1.2)

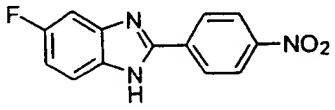
(1) 2-(N-Cyclohexanecarbonyl-4-aminophenyl)-5-trifluoromethyl benzimidazole was prepared from the amine, 2-(4-aminophenyl)-5-trifluoromethyl benzimidazole (1.2; see above). The amine (0.239 g, 0.86 mmol) was dissolved in THF:H_2O (5 ml, 1:1) followed by K_2CO_3 (0.1213 g, 0.88 mmol) and cyclohexyl carbonyl chloride (130 μL, 0.95 mmol). The reaction mixture was shaken for 23 h at room temperature. Sodium chloride was added to the reaction and the mixture extracted with EtOAc. The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated under vacuum. The resulting solid was purified by preparative TLC (10% MeOH in CH_2Cl_2).



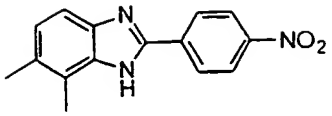
(1)

The next species (2), 2-(N-cyclohexanecarbonyl-4-aminophenyl)-5-fluoro benzimidazole was synthesized from the following series of benzimidazole intermediates: 1) 2-(4-nitrophenyl)-5-fluoro benzimidazole (designated 2.1) and 2) 2-(4-aminophenyl)-5-fluoro benzimidazole (designated 2.2).

(2.1) 2-(4-Nitrophenyl)-5-fluoro benzimidazole was synthesized as follows: 1,2-diamino-4-fluorobenzene (1.26 g, 10.0 mmole was mixed with 4-nitrobenzoic acid (1.67 g, 9.8 mmole) and dissolved in $POCl_3$ (10 ml) and heated to reflux for 2.5 hours. The reaction mixture was cooled and cautiously poured onto ice. The resulting solid was filtered, washed with $NaHCO_3$ and used without further purification.

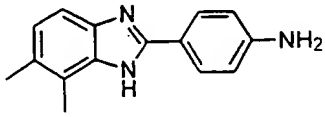


(2.1)



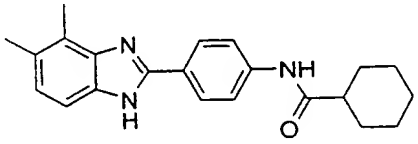
(3.1)

(3.2) 2-(4-Aminophenyl)-4,5-dimethyl benzimidazole was synthesized by dissolving 1 g of the above nitrobenzimidazole (3.1) in 30% $Na_2S \cdot 9H_2O$ (20 ml) and stirring at RT for 2.5h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate and concentrated under vacuum. The product was characterized by mass spectroscopy.



(3.2)

(3) 2-(N-Cyclohexanecarbonyl-4-aminophenyl)-3,4-dimethyl benzimidazole was prepared by dissolving 0.0954 g (0.402 mmol) of the above amine (3.2) in 1 ml of pyridine followed by cyclohexanecarbonyl chloride (57.6 µl) and heated to 60° C overnight. The reaction was diluted with water (8 ml) and extracted with EtOAc. The combined organic fractions were combined, dried (Na_2SO_4) and concentrated under vacuum. The resulting solid was purified by flash chromatography (5% $MeOH/CH_2Cl_2$).



(3)

IgE Down-Regulatory Activity

All of the disclosed species were tested for their ability to suppress IgE in both the *ex vivo* and *in vivo* assays. They were all active in both assays. Activities (IC_{50}) of the species in the *ex vivo* assay ranged from about 100 pM to 1 nM. In the *in vivo* assay, the IC_{50} dose ranged from approximately 100 µg/kg body weight/day to about 10 mg/kg body weight/day. The diacyl benzimidazole compounds were generally more potent than the monoacyl compounds.

systemic dosing of the active compound. The compositions of pharmaceutical formulations are well known in the art. The treatment regimen preferably involves periodic administration. Moreover, long-term therapy may be indicated where allergic reactions appear to be triggered by continuous exposure to the allergen(s). Daily or twice daily administration has been effective in suppressing the IgE response to a single antigen challenge in animals when carried out continuously from a period of two to seven consecutive days. Thus, in a preferred embodiment, the compound is administered for at least two consecutive days at regular periodic intervals. However, the treatment regimen, including frequency of dosing and duration of treatment may be determined by the skilled practitioner, and modified as needed to provide optimal IgE down-regulation, depending on nature of the allergen, the dose, frequency, and duration of the allergen exposure, and the standard clinical indices.

In one embodiment of the present invention, an IgE-suppressing compound may be administered in conjunction with one or more of the other small molecule inhibitors disclosed, in order to produce optimal down-regulation of the patient's IgE response. Further, it is envisioned that one or more of the compounds of the present invention may be administered in combination with other drugs already known or later discovered for treatment of the underlying cause as well as the acute symptoms of allergy or asthma. Such combination therapies envisioned within the scope of the present invention include mixing of one or more of the small molecule IgE-inhibitors together with one or more additional ingredients, known to be effective in reducing at least one symptom of the disease condition. In a variation, the small molecule IgE-inhibitors herein disclosed may be administered separately from the additional drugs, but during the same course of the disease condition, wherein both the IgE-inhibitor(s) and the palliative compounds are administered in accordance with their independent effective treatment regimens.

While a number of preferred embodiments of the invention and variations thereof have been described in detail, other modifications and methods of use will be readily apparent to those of skill in the art. Accordingly, it should be understood that various applications, modifications and substitutions may be made of equivalents without departing from the spirit of the invention or the scope of the claims.

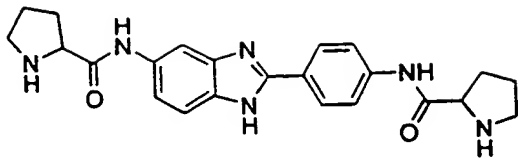
wherein Y is selected from the group consisting of mono, di, and tri substituted H, alkyl, alkoxy, aryl, substituted aryl, hydroxy, halogen, amino, alkylamino, nitro, cyano, CF_3, OCF_3, $CONH_2$, CONHR and $NHCOR_1$;

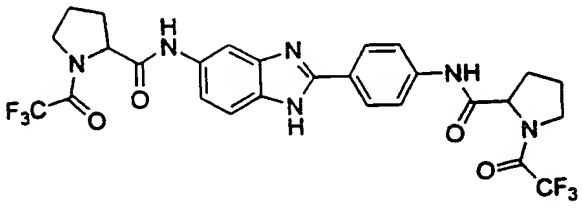
wherein R_1 is selected from the group consisting of alkyl, cycloalkyl substituted cycloalkyl, multi-ring cycloalkyl, fused-ring aliphatic, cyclopropyl, substituted cyclopropyl, cyclobutyl, substituted cyclobutyl, cyclopentyl, substituted cyclopentyl, cyclohexyl, substituted cyclohexyl, cycloheptyl, substituted cycloheptyl, bicycloheptyl, bicyclooctyl, bicyclononyl, substituted bicycloalknyl, adamantyl, substituted adamantyl and the like.

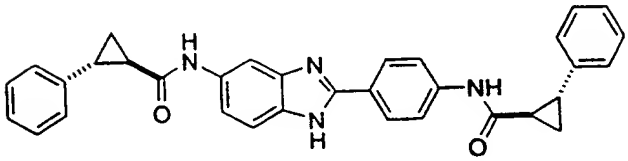
2. The pharmaceutical composition of claim 1, wherein the R_1 and R_2 substitutions are selected from the group consisting of alkyl, aryl, CF_3, CH_3, OCH_3, OH, CN, COOR and COOH.

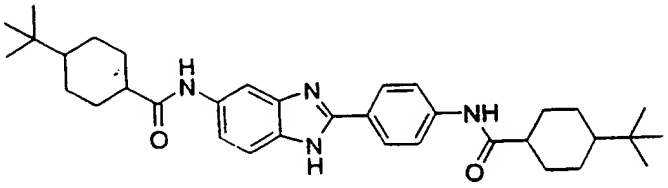
3. The pharmaceutical composition of Claim 1, wherein the compound is from genus A.

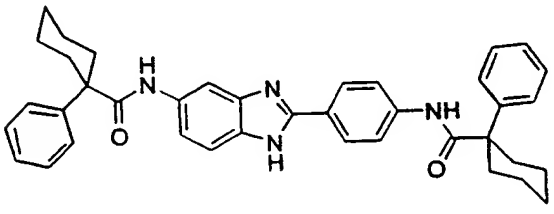
4. The pharmaceutical composition of Claim 3, wherein the compound is selected from the group consisting of:

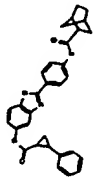


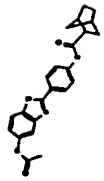


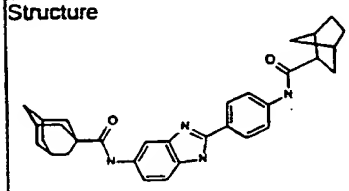


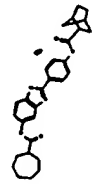


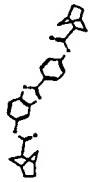


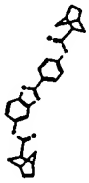
Structure	BIQM
	$C_{31}H_{30}N_4O_2$
	CLOGP 6.04

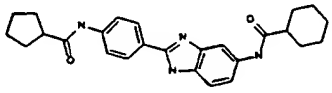
Structure	BIQN
	$C_{23}H_{24}N_4O_2$
	CLOGP 4.27

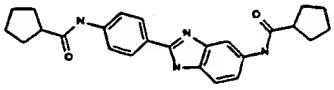
Structure	BIQO
	$C_{32}H_{36}N_4O_2$
	CLOGP 6.93

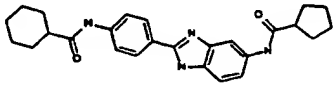
Structure	BIQP
	$C_{29}H_{34}N_4O_2$
	CLOGP 6.86

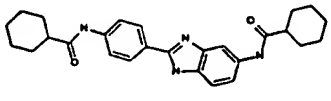
Structure	BIQQ
	$C_{29}H_{32}N_4O_2$
	CLOGP 6.06

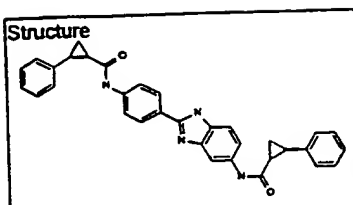
Structure	BIQR
	$C_{29}H_{30}N_4O_2$
	CLOGP 5.58

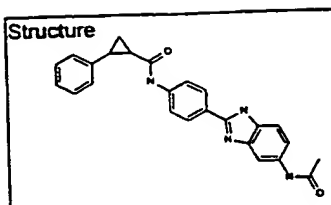
Structure	BIJI
	$C_{26}H_{30}N_4O_2$
	CLOGP 5.99

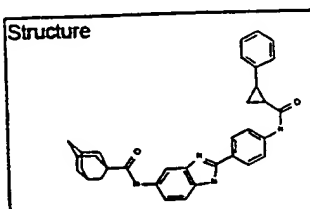
Structure	BIJJ
	$C_{25}H_{28}N_4O_2$
	CLOGP 5.43

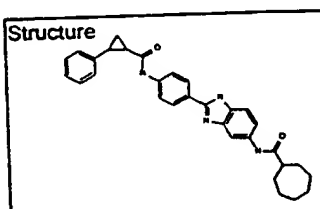
Structure	BIIJ
	$C_{26}H_{30}N_4O_2$
	CLOGP 5.99

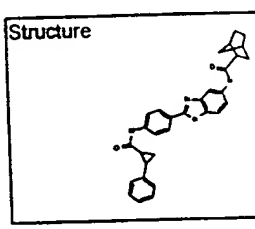
Structure	BIII
	$C_{27}H_{32}N_4O_2$
	CLOGP 6.55

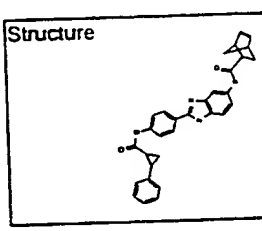
Structure	BIMM
	$C_{33}H_{28}N_4O_2$
	CLOGP 6.01

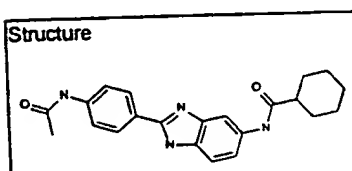
Structure	BIMN
	$C_{25}H_{22}N_4O_2$
	CLOGP 4.25

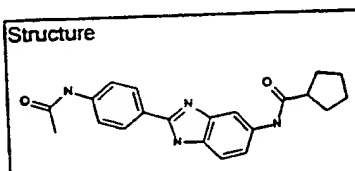
Structure	BIMO
	$C_{34}H_{34}N_4O_2$
	CLOGP 6.91

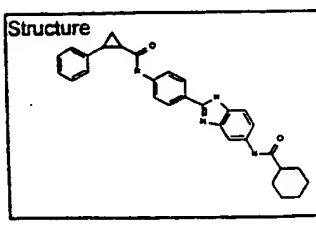
Structure	BIMP
	$C_{31}H_{32}N_4O_2$
	CLOGP 6.84

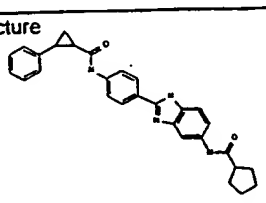
Structure	BIMQ
	$C_{31}H_{30}N_4O_2$
	CLOGP 6.04

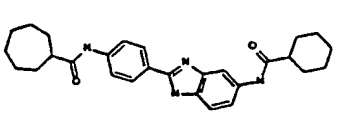
Structure	BIMR
	$C_{31}H_{28}N_4O_2$
	CLOGP 5.55

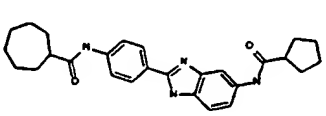
Structure	BINI
	$C_{22}H_{24}N_4O_2$
	CLOGP 4.52

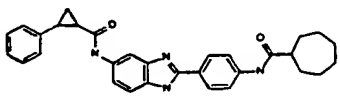
Structure	BINJ
	$C_{21}H_{22}N_4O_2$
	CLOGP 3.96

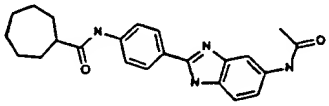
Structure	BIMI
	$C_{30}H_{30}N_4O_2$
	CLOGP 6.28

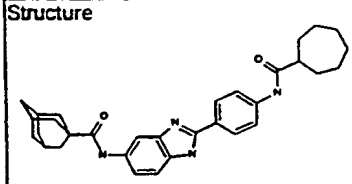
Structure	BIMJ
	$C_{29}H_{28}N_4O_2$
	CLOGP 5.72

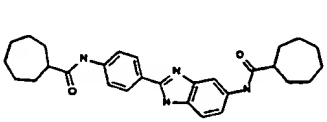
Structure	BIPI
	$C_{28}H_{34}N_4O_2$
	CLOGP 7.11

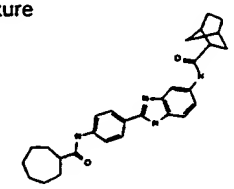
Structure	BIPJ
	$C_{27}H_{32}N_4O_2$
	CLOGP 6.55

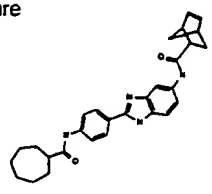
Structure	BIPM
	$C_{31}H_{32}N_4O_2$
	CLOGP 6.84

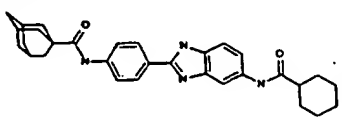
Structure	BIPN
	$C_{23}H_{26}N_4O_2$
	CLOGP 5.08

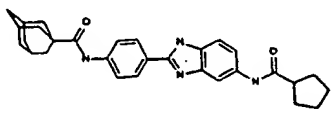
Structure	BIPO
	$C_{32}H_{38}N_4O_2$
	CLOGP 7.74

Structure	BIPP
	$C_{29}H_{36}N_4O_2$
	CLOGP 7.67

Structure	BIPQ
	$C_{29}H_{34}N_4O_2$
	CLOGP 6.86

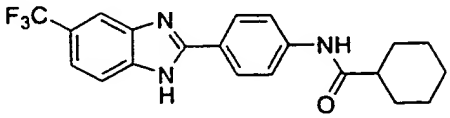
Structure	BIPR
	$C_{29}H_{32}N_4O_2$
	CLOGP 6.38

Structure	BIOI
	$C_{31}H_{36}N_4O_2$
	CLOGP 7.18

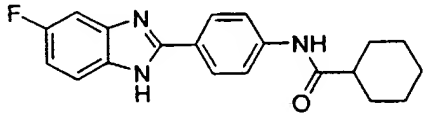
Structure	BIOJ
	$C_{30}H_{34}N_4O_2$
	CLOGP 6.62

5. The pharmaceutical composition of Claim 1, wherein the compound is from genus B.

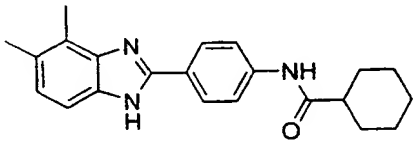
6. The pharmaceutical composition of Claim 5, wherein the compound is selected from the group consisting of:



(1)



(2)



(3)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11490

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 719 765 A (MITSUI TOATSU CHEMICALS) 3 July 1996 (1996-07-03) page 20-54; claims ---	1-5,7
X	WO 98 17267 A (HURLEY LAURENCE H ;KONTOYIANNI MARIA (US); UNIV TEXAS AUSTIN (US);) 30 April 1998 (1998-04-30) figure 82/146: compound 895-6643 ---	1-3,5,7
X	ASHTON ET AL: "now low-density lipoprotein receptor upregulators acting via a novel mechanism" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, 1 January 1996 (1996-01-01), pages 3343-3356, XP002086153 ISSN: 0022-2623 page 3348, table 4, compounds 25 and 26 ---	1,2,5,7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 1999	15/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Orviz Diaz, P

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/US 99/ 11490

Box I Observations where certain claims wer found unsearchabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/11490

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0719765 A	03-07-1996	JP 8231514 A	10-09-1996
		US 5821258 A	13-10-1998
WO 9817267 A	30-04-1998	AU 4988997 A	15-05-1998
		US 5939444 A	17-08-1999
		US 5922753 A	13-07-1999
		US 5919808 A	06-07-1999
EP 0700906 A	13-03-1996	US 5496826 A	05-03-1996
		AU 695891 B	27-08-1998
		AU 3039995 A	14-03-1996
		JP 8073438 A	19-03-1996